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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER

ART UNIT	PAPER NUMBER
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DATE MAILED:

24

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.
08/812,393

Applicant(s)
Sherman et al.

Examiner
Wilson, Michael C.

Group Art Unit
1633



☒ Responsive to communication(s) filed on Jun 20, 2000

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-21 is/are pending in the application.

Of the above, claim(s) 6-21 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-5 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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DETAILED ACTION

Applicant's arguments filed 5-9-00, paper number 23, have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-21 are pending. Claims 6-21 remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected inventions. Election was made **without** traverse in Paper No. 20. Claim 1-5 are under consideration in the instant application.

Claim Rejections - 35 USC § 112

1. Claims 1-5 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a preparing a nucleic acid molecule encoding a mouse T-cell receptor (TCR) which recognizes an antigen comprising administering the antigen to a transgenic mouse whose genome comprises a nucleic acid sequence encoding human HLA-A2 molecule wherein said mouse functionally expresses HLA-A2 on the surface of antigen presenting cells so as to allow presentation of the antigen with an HLA-A2 molecule such that recognition of the antigen and HLA-A2 molecule by cytotoxic T lymphocytes (CTL) occurs, isolating the CTL from the mouse, creating antigen-specific CTL populations and isolating the nucleic acid molecule encoding antigen-specific TCR using RT-PCR, does not reasonably provide enablement for preparing a nucleic acid molecule encoding a human HLA-restricted TCR specific for a TAA

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using any transgenic non-human vertebrate by cloning or amplifying a nucleic acid molecule as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In claim 1, the only step in the method of preparing an isolated nucleic acid molecule comprises "cloning or amplifying a nucleic acid molecule..." prepared by "immunizing..." wherein the immunizing results in the isolation of a nucleic acid molecule. The cloning/amplifying step does not result in isolation of a nucleic acid molecule. The preamble does not reflect the body of the claim because the cloning/amplification step does not result in isolation of a nucleic acid molecule. Nor do the method steps flow logically to result in the isolation of the nucleic acid molecule of interest because cloning/amplifying is performed after recovering the CTL. In fact, it is not clear from the method steps claimed whether the isolation step is the cloning/amplification step. The method is also missing steps. The omitted steps are: isolating the CTL from the mouse, and creating antigen specific CTL populations *in vitro* which recognize the antigen. Therefore the claim does not provide the appropriate logical flow of steps required to isolate nucleic acids as claimed.

Claim 1 recites the limitation of a transgenic non-human mammal or avian which is modified so as to express at least one human HLA antigen. The state of the art of transgenics at the time of filing was and continues to be unpredictable. The individual gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct, the site

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of integration, etc. are all important factors in controlling the expression of the transgene. Wall (1996, *Theriogenology*, Vol. 45, pages 57-68) discloses the unpredictability of transgene behavior due to factors such as position effect and unidentified control elements resulting in a lack of transgene expression or variable expression (paragraph bridging pages 61-62). Ebert et al. (1988, *Mol. Endocrinology*, Vol. 2, pages 277-283) teach a transgene encoding the human somatotropin gene operably linked to the mouse metallothionein promoter caused different phenotypes in transgenic pigs and mice (page 277, column 2, lines 17-27). Therefore, one of skill could also not predict whether a transgene expressed in a transgenic mouse will be expressed similarly or cause a similar phenotype in other non-human mammals or in avians. In fact, Overbeek (1994, "Factors affecting transgenic animal production," *Transgenic animal technology*, pages 96-98) teaches that within one litter of transgenic mice, considerable variation in the level of transgene expression occurs between founder animals and causes different phenotypes (page 96, last paragraph).

The specification teaches using A.2.1/KbxCD8 or A2.1 transgenic mice (page 9, line 11) but does not provide any guidance how to make any other transgenic non-human mammals or avians. Given the differences in the expression of a transgene within a litter of transgenic mice and between transgenic mice and other non-human mammals or avians, taken with the mere reference to the transgenic mice provided in the specification, it would have required undue experimentation to extend the transgenic mice referred to in the specification to other HLA molecules, to other non-human mammals, to avians or to other phenotypes. Applicants argue the transgenic source is not critical to the invention. However, the specification and the art at the

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time of filing does not enable any transgenic non-human mammal or avian other than the transgenic mouse referenced which was known in the art at the time of filing. Given the unpredictability in the art at the time of filing regarding transgenics, it would have required one of skill undue experimentation to determine the parameters required to make/use any transgenic non-human mammal or avian with the phenotype required to obtain the nucleic acid molecule of interest as claimed.

Claim 1 recites obtaining any non-human TCR from any non-human transgenic mammal or avian. This encompasses obtaining a rabbit TCR from avians. Applicants have only enabled obtaining mouse TCR from transgenic mice because applicants do not teach how to obtain a TCR of one species from transgenic non-human mammal or avian of different species.

Claim 1 recites a transgenic non-human mammal or avian which is modified so as to express at least one human HLA antigen. The entire HLA molecule must be expressed on the surface of an antigen-presenting cell to be of use in the instant invention. In addition, a cell expressing only one human HLA molecule is not of use in the instant invention. The HLA molecules must be expressed to significant levels such that antigen recognition can occur and CTL that recognize the antigen can be generated. Without adequate levels of HLA expression and production of CTL that recognize the administered antigen, the transgenic non-human mammal or avian claimed is of no use.

Claim 1 as newly amended recites a number of HLA-A2-restricted antigens. The specification only teaches transgenic mice expressing human HLA-A2. Given the unpredictability

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in the transgenic art as discussed above and the teachings in the disclosure, it would have required one of skill undue experimentation to determine the parameters required to use any other HLA molecules with Her-2/neu, RAS, p53, tyranase, MART, Gp100, Mage, Bage, or MUC-1.

Therefore, claim 1 should be limited HLA-A2-restricted CTL and a transgenic animal modified to express HLA-A2.

2. Claims 1-5 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, the only step claimed in the method of preparing an isolated nucleic acid molecule comprises "cloning or amplifying a nucleic acid molecule..." prepared by "immunizing..." wherein the immunizing results in the isolation of a nucleic acid molecule. The cloning/amplifying step does not result in isolation of a nucleic acid molecule. The preamble does not reflect the body of the claim because the cloning/amplification step does not result in isolation of a nucleic acid molecule. Nor do the method steps flow logically to result in the isolation of the nucleic acid molecule of interest because cloning/amplifying is performed after recovering the CTL. In fact, it is not clear from the method steps claimed whether the isolation step is the cloning/amplification step. The method is also missing steps. The omitted steps are: isolating the CTL from the mouse, and creating antigen specific CTL populations *in vitro* which recognize the antigen. Therefore the claim does not provide the appropriate logical flow of steps required to isolate nucleic acids as claimed and is indefinite.

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Claim 1 is indefinite because it is unclear from the phrase "encoding at least one of the variable regions of the α and β chains" whether applicants intend to claim at least one variable region which can be either α or β chain or whether applicants intend to claim at least one α chain and one β chain.

Claim 1 is indefinite because the phrase "to Lys tumor cells" is unclear. It is unclear whether applicants intend to claim lysing tumor cells or some other parameter.

Claim 5 is indefinite because the term "essentially" is not defined in the specification such that the essential elements of the primers could be determined. While the term "essentially" may be used in claim language, in the instant claims the metes and bounds of the claim cannot be determined because it is not clear which primers or what portions of the primers are considered essential to the invention.

Claim Rejections - 35 USC § 103

3. Claims 1-5 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Man et al. (1994, J. Immunol., Vol. 153, pages 4458-4467) in view of Cole et al. (April 1995, FASEB Journal, Vol, 9 page A801, abstract 4638).

Man et al. teach administering the influenza A antigen, M1₍₅₈₋₆₆₎, to transgenic mice expressing HLA-A2.1 and obtaining cytotoxic T cells which recognize the M1 (page 4459, column 1, "influenza-specific CTL from HLA-A2.1 transgenic mice"). The nucleic acid molecule encoding the α and β chain of the TCR were isolated by PCR (page 4459, column 2, "PCR

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amplification and sequencing of TCR α - and β -chain cDNA). The primers used by Man et al. were mouse α and β TCR-specific primers V β 8, V β 5 and V β 6. The primers taught by Man et al. are essentially the which are essentially the primers V β 8.1, V β 8.2, V β 8.3, V β 5.1 and V β 6 primers in Fig. 6. because the primers share homology and both serve the essential function of identifying the V β 8, V β 5 and V β 6 chains of the TCR. Man et al. does not teach using the transgenic mouse to identify tumor associated antigens. However, at the time of filing a number of tumor associated antigens which were HLA-A2 restricted were known in the art at the time of filing and could have replaced the M1₍₅₈₋₆₆₎. For example, Cole et al. teach the melanoma associated antigen MART-1 which is recognized by CTL in an HLA-A2 restricted manner. Cole et al. teach generating MART-1-specific, HLA-A2 restricted CTL and isolating the TCR gene from the CTL (see entire abstract). Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the method of isolating TCR genes from transgenic mice taught by Man et al. to obtain TCR genes specific for the MART-1 antigen. Motivation to isolate TCR genes from TAA-specific CTL is provided by Cole et al. by teaching obtaining CTL which are specific for MART-1 and isolating the TCR receptors which are specific for MART-1 antigen (line 6). One of ordinary skill would have been motivated to replace the M1 antigen with the MART-1 antigen to obtain MART-1 specific TCR *in vivo*.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into

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account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, motivation to isolate TCR genes from TAA-specific CTL is provided by Cole et al. by teaching obtaining CTL which are specific for MART-1 and isolating the TCR receptors which are specific for MART-1 antigen (line 6). One of ordinary skill would have been motivated to replace the M1 antigen with the MART-1 antigen to obtain MART-1 specific TCR *in vivo*.

Conclusion

4. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.


No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson whose telephone number is (703) 305-0120. The examiner can normally be reached on Monday through Friday from 8:30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. The fax phone number for this Group is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 305-0196.

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